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Deciphering the Central Dogma of Telomere: New Beginnings

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Abstract

Telomeres have always been an enigmatic structure since their discovery. The unravelling of new findings and changing concept of central dogma at telomeres have intrigued the telomere biologists further. Telomeres have been considered antennas for various environmental stress and detectors of cellular DNA damage. The translation of mammalian telomeres has further raised many questions about its involvement in maintaining the genomic integrity and have opened doors for new era of research in telomere biology and telomere-related diseases. Unravelling the mysteries of telomeric organization and its regulation will have widespread impact in various fields including cancer treatment, space exploration and aging disorders.

Keywords: Telomeres • Shelterin complex • TERRA • Chromosome ends • Long non-coding RNA • Genomic integrity • DNA damage response

Introduction

Human telomeres are functionally and architecturally unique structures which were embraced to deal with the evolutionary challenges from circular to linear DNA. Their complex 'knot-like' structure acts as buffer and prevent the coding regions of genome from being eroded during each round of replication. They also guard the chromosomal ends from being identified as strand breaks and prevent end-fusions. The six proteins (TRF1, TRF2, TIN2, POT1, TPP1 and RAP1) together known as shelterin complex, binds with telomeric DNA and acts like a glue to keep telomeric structure intact and maintain the genomic stability [1]. Telomeres are known to be heterogeneous in length with considerable variation observed between different tissues and chromosomes [2,3]. Although telomeres occupy a very small portion of the whole genome, they are known to get shortened with age and accumulated DNA damage, hence play a critical role in ageing, cancer progression and neurodegenerative diseases [4].

Are telomeres transcriptionally active?

Until a few years back, just like the centromeres, telomeres were also considered as transcriptionally inactive regions. However, the evidence of mammalian telomeric transcription and subsequent discovery of telomere repeat containing RNA transcripts known as TERRA (TElomeric Repeat-containing RNA), brought a paradigm shift in telomere biology [5,6]. TERRA are 200 bases to 10 kilo bases long sequences transcribed from telomeric and sub-telomeric regions of chromosomes and consists of UUAGGG repeats. TERRAs are involved in maintaining telomere homeostasis and regulate telomerase activity [7]. TERRAs interacts with different chromatin remodeling complexes to regulate the dynamics of chromatin structure at telomeric ends and further regulate the expression of several genes involved in multiple biological processes involved in maintaining of telomere structure [8].

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Translation of telomere RNAs

Telomeres are enriched in heterochromatin marks and epigenetic nature of human telomeres still remains elusive [9]. Hence, after unearthing the presence of long non-coding-RNAs transcribed from telomere, it was believed that TERRAs are not translated in to any functional protein due to repetitive nature of its sequences and lack of start codons. However, recently, in an interesting development, Al-Turki TM and Griffith JD [10] have for the first time reported that mammalian TERRA is indeed translated to generates two dipeptides repeat proteins made up of repeating valine–arginine (VR)n and Glycine Leucine (GL)n residues. They hypothesized a non-ATG translation mechanism (RAN) for the generation of these dipeptide proteins. It has been shown that terra di-peptide proteins are of varying length and longer proteins are found to aggregate in the nucleus. Further, it has been demonstrated that under normal conditions, the level of TERRA and these di-peptide proteins (di-peptides) are maintained at a low level in cytoplasm but produced in large amounts under telomeric stress. However, the molecular switch behind this response needs to deciphered.

Plausible roles of translated telomere

In the recent times, with the advent of high throughput techniques, many novel long non-coding RNAs (lncRNAs) have been identified. Lnc RNAs were initially thought to be a group of non-protein coding regulatory molecules that are involved in transcriptional and post-transcriptional regulation of gene expression, chromatin remodeling, DNA damage response, regulating organelle functions and genome integrity [11]. In the past few years, several groups have reported that lnc RNAs can actually encode proteins both in mammalian systems and plants [12,13]. These encoded proteins are thought to be the source for novel bio-peptides and could be the part of evolution process [14,15]. These are also reported to be involved in pathogenesis of many diseases including different cancers.

Recent discovery that TERRA can be translated into di-peptide repeat protein would unravel novel mechanisms of telomere functioning in mammalian cells. Accumulation of TERRA di-peptide may impact various biological pathways including nucleic acid metabolism, repair, protein synthesis, inflammation and genomic instability [10].

Translation of TERRA may provide an additional advantage of stability and greater versatility at carrying out cellular functions. A translated TERRA protein may bind to Transcription Factor Binding Sites (TFBS) to regulate gene expression and may also play a role as an anchor to facilitate interaction between Chromatin Remodeling Complexes (CRC), telomere shelterin protein, DNA repair and stress response proteins at DNA damage sites. However, exact functional role of TERRA proteins still needs to be explored and hold great promises for future (Figure 1).

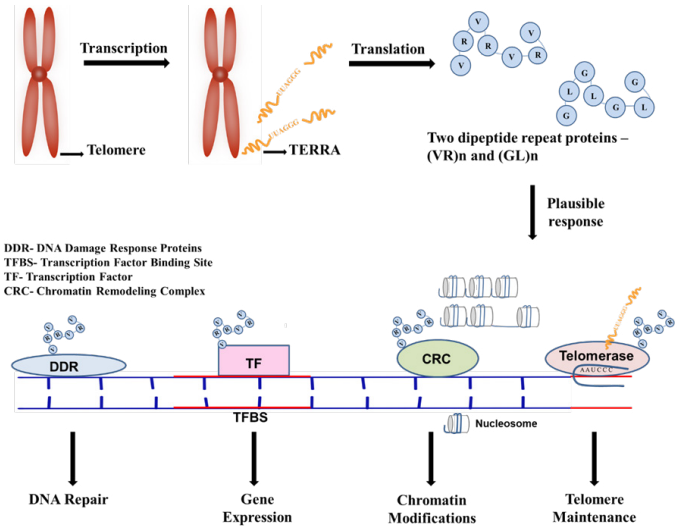

Figure 1. Illustration showing translation of telomere RNA (TERRA) and its plausible role in multiple cellular functions.

Future Outlook

Developments in the field of telomere biology are very rapid and dynamic. Current understanding of Human telomere structure and its function is constantly evolving. In the last decade itself, telomeres have undertaken a remarkable journey from being known as “transcriptionally inactive” to a recently discovered “translated protein”. These findings will have far-reaching impact on DNA repair, ageing and cancer research.

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Conflict of Interest

None.

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